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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/715,729	SOMMADOSSI ET AL.	
	Examiner	Art Unit	
	Louise Humphrey, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33,34,37-52 and 87-108* is/are pending in the application.

4a) Of the above claim(s) *38,41-47,51,52,87,88,90,91 and 93-99* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33,34,37,39,40,48-50,89,92 and 100-108* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 October 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/4/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Office acknowledges the receipt of Applicants' election and Amendment, filed on 04 May 2007. Applicants elect the following:

Group I, claims 33, 34, 37, 38, 48-52 and 87-108;

The species of 3'-L-valinyl-β-D-2'-methyl-cytidine; and

claim 50 (iv) and L= CH, E=CH, W=O.

Applicants did not state whether the election was made with traverse. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-32, 35, 36, 53-86 have been cancelled. Claims 33, 34, 37-52, and 87-108 are pending. Claims 38, 41-47, 51, 52, 87, 88, 90, 91 and 93-99 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 04 May 2007.

Claims 33, 34, 37, 39, 40, 48-50, 89, 92 and 100-108 are examined.

Information Disclosure Statement

An initialed and dated copy of Applicant's IDS form 1449, filed on 04 March 2004, is attached to the instant Office action.

Double patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 33, 34, 37, 39, 40, 48-50, 89, 100, and 105 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 4 of U.S. Patent No. 7,192,936 B2. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are anticipated by claim 4 of U.S. Patent No. 7,192,936 B2. The instant claims encompass the previously claimed method.

Claims 33, 34, 37, 39, 40, 48-50, 89, 100, and 105 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 15 and 18 of U.S. Patent No. 7,169,766 B2. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are

anticipated by claims 15 and 18 of U.S. Patent No. 7,169,766 B2. The instant claims are generic to the patented claim, in other words, claims 15 and 18 of U.S. Patent No. 7,169,766 B2 is a species of the instant claims.

Claim Rejections - 35 USC § 112, 1st ¶, written description

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 33, 34, 37, 39, 40, 48-50, 89, 92 and 100-108 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The factors considered in the Written Description requirement are (1) *level of skill and knowledge in the art*, (2) *partial structure*, (3) *physical and/or chemical properties*, (4) *functional characteristics alone or coupled with a known or disclosed correlation between structure and function*, and the (5) *method of making the claimed invention.* Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." M.P.E.P. §2163.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, at the time the invention was made, of the specific subject matter claimed. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); *In re Gostelli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 199 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In *Regents of the University of California v. Eli Lilly & Co.,* the court indicated that, while applicants are not required to disclose every species encompassed by a genus, the description of the genus is achieved by the recitation of a representative number of species falling within the scope of the claimed genus. Although the M.P.E.P. does not define what constitutes a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad genus. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

In the instant case, the claims are directed to a method for treating a *Flaviviridae* infection in a host comprising administering a 2'-branched nucleoside, or its pharmaceutically acceptable prodrug or salt to the host, in combination and/or alternation with one or more drugs that directly or indirectly induce a mutation in a Flaviviridae at a location other than a mutation of a nucleotide that results in a change from serine of domain of the RNA polymerase region. The limitation "one or more drugs that directly or indirectly induce a mutation in a Flaviviridae at a location other than a mutation of a nucleotide that results in a change from serine of domain B of the RNA polymerase (NS5B) region" encompass all small molecule compounds, proteins, nucleic acid, structural homologs, and synthetic analogs or functional equivalents. Thus, the claims encompass an inordinate number of unspecified species that are neither described nor contemplated by Applicants.

Applicants have not conveyed possession of the invention with reasonable clarity to one skilled in the art. The specification only provides description for the opposite: drugs that are associated with a mutation at a nucleotide that encodes for serine in the NS5B region (page 11, line 4-13). However, there is no identification of any particular structure that correlates with the specifically claimed function of directly or indirectly inducing a mutation in a Flaviviridae at a nucleotide location other than the serine mutation in the NS5B region. Moreover, the specification lacks sufficient variety of species to reflect this variance in the genus since the specification does not provide any examples of drugs that induce a mutation at a nucleotide other than the serine mutation in the NS5B conserved region.

The instant application is highly analogous to the *University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886 (Fed. Cir. 2004). Patent is directed to a method for inhibiting prostaglandin synthesis in human host using unspecified compound. Action by University of Rochester against G.D. Searle & Co. Inc., Monsanto Co., Pharmacia Corp., and Pfizer Inc. for patent infringement. District court granted defendants' motion for summary judgment of patent invalidity based on failure to satisfy written description and enablement requirements, and plaintiff appealed. Affirmed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states: "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* on page 1116).

The skilled artisan cannot envision the detailed chemical structures of the unspecified compounds in the claimed method. The specification is devoid of any description of the representative chemical compounds that qualify for the functional characteristics claimed. As a result, one of skill in the art could not conclude that Applicant was in possession of the claimed methods at the time of the invention. Therefore, claims 33, 34, 37, 39, 40, 48-50, 89, 92 and 100-108 do not meet the written description provision of 35 U.S.C. §112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variable.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (page 1115).

Claim Rejections - 35 USC § 112, 1st ¶, scope of enablement

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 33, 34, 37, 39, 40, 48-50, 89, 92 and 100-108 are rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for a method for treating a HCV infection comprising administering a 2'-branched nucleoside in combination with interferon α and ribavirin, levovirin, or viramidine, does not reasonably provide enablement for the following:

(1) a method for treating any other *Flaviviridae* infection; and

(2) a method for treating HCV infection comprising administering, without interferon α, 2'-branched pyrimidine nucleoside or its prodrug in combination with one or more drugs that directly or indirectly induce a mutation other than a change from serine in the NS5B conserved region in a *Flaviviridae* virus.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors

(MPEP §2164.01(a)). See, *In re Wands*, 8 USPQ2d 1400, at 1404 (CAFC 1988); and *Ex Parte Forman*, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered.

Nature of the invention. The claims are drawn to a method for treating a Flaviviridae infection in a host comprising administering a 2'-branched nucleoside, or its pharmaceutically acceptable prodrug or salt to the host, in combination and/or alternation with one or more drugs that directly or indirectly induce a mutation other than the serine mutation in the highly conserved consensus sequence, XRXSGXXXT, of NS5B.

The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

Breadth of the claims. The breadth of the claimed invention is exceedingly large and fails to receive adequate support in the specification. The broad claims encompass treatment in any host of infection by any and all viruses of the *Flaviviridae* family, including yellow fever virus, dengue fever virus, West Nile virus, Japanese encephalitis virus, classical swine fever virus, border disease virus, bovine viral diarrhea virus (BVDV) and HCV. The claims are not limited to the administration of a single drug

combination, encompassing the use of a wide variety of unspecified drugs to be administered in combination or alternation with any 2'-branched nucleoside or its prodrug.

Working examples. The disclosure fails to provide any working embodiments that meet the claimed limitations. While there is one cell culture example for the species of BVDV, entailing treating the BVDV-infected MDBK cell with the 2'-β-D-CH_3-riboC. There are no examples of the combination drugs that induce a mutation other than a change from serine in the NS5B region. No *in vivo* working example of treatment with any compound is disclosed in the specification.

Guidance in the specification. 1) The claims do not provide any structural limitations for drugs that induce a mutation other than a change from serine in the NS5b region. Thus, any chemical compound, including *inter alia*, organic compounds, peptide mimetics, and antibodies, may be encompassed by the claims. However, the specification fails to guide the skilled artisan toward those compounds that can reasonably be expected to retain the desired inhibitory activity. 2) The specification does not teach therapeutic effects of 2'-branched nucleosides in any host. The *in vitro* data show that BVDV can develop resistance to 2'-β-D-CH_3-riboC based on the viral rebound in the treated cell culture sample (Figure 4) even in combination with interferon-α-2b. There is no working example of any other Flavivirus or of 2'-β-D-CH_3-riboC in combination or alternation with any other drug compounds. Thus, the disclosure does not relate to the claimed medical treatment against any *Flaviviridae* viral disease in any subject, especially in humans.

State of the prior art. 3) The current state of the art teaches that interferon-α-2b is indispensable in the combination therapy for HCV infection (Afdhal, 2005; Zhou, 2005; Gerotto, 1999; Hu, 2001). 4) The claimed invention has the same pitfall as AIDS treatment. Similar to HIV reverse transcriptase, the molecular target of the claimed invention, NS5B polymerase, replicates rapidly with a high mutational frequency and creates diverse 'quasispecies' under drug-selective pressures (Gerotto, 1999; Hu, 2001). Rapid viral replication and its inherent genetic diversity will certainly culminate drug resistance to any NS5B inhibitors. Therefore, iterative drug design and combination therapies of drugs that intervene with different steps in the HCV replicative cycle are needed to combat the viral infection (Wu, 2003). There is no evidence that shows any correlation of *in vitro* testing with *in vivo* efficacy. Analogous to HIV therapeutic experiments, an i*n vitro* testing is, at most, useful tool for screening potential anti-viral agents but is not predictive of *in vivo* effectiveness. *Ex parte Balzarini* (BdPat App&Int) 21 USPQ2d 1892. One skilled in the art would not associate successful *in vitro* testing results with successful *in vivo* treatment due to the high level of unpredictability of the art. Therefore, the art of HCV treatment using NS5B polymerase inhibitors is highly unpredictable from *in vitro* data of a simple cell culture experiment showing the dose response of a single drug compound.

Amount of experimentation necessary. 5) The disclosure fails to provide sufficient working embodiments to enable the breadth of the claimed invention. 6) Legal precedence dictates that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification. *In re Fisher*, 427 F.2d 833, 839,

166 U.S.P.Q. 18 24 (C.C.P.A. 1970). *In re Vaeck*, 20 U.S.P.Q.2d 1438 (C.A.F.C 1991). *In re Angstadt*, 537 F.2d 498, 502-03, 190 U.S.P.Q. 214, 21 (C.C.P.A. 1976). Thus, when all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 33, 34, 37, 48-50, 92, 104, 107 and 108 are rejected under 35 U.S.C. §102(e) as being anticipated by Carroll *et al.* (US 7,105,499 B2, priority filing date 22 January 2001).

The instant claims are directed to a method for treating a *Flaviviridae* infection in a host comprising administering a 2'-branched nucleoside, or its pharmaceutically acceptable prodrug or salt to the host, in combination and/or alternation with one or more drugs that directly or indirectly induce a mutation in a Flaviviridae at a location other than a mutation of a nucleotide that results in a change from serine of domain of the RNA polymerase region (NS5B).

Carroll *et al.* teaches a method of treating RNA-dependdent RNA viral infection or Flaviviridae viral infection, more specifically, an HCV infection, by administering a compound like 2'-methyl-cytidine (column 15, line 14-67), in combination or alternation

with other agents like ribavirin, viramidine, levovirin and interferon-α-2b (column 32). Thus, the instant invention is anticipated by Carroll *et al.*

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 39, 40, 89, 100-103, 105 and 106 are rejected under 35 U.S.C. §103(a) as being unpatentable over Carroll *et al.* (US 7,105,499 B2) in view of Sinko *et al.* (1998).

The instant invention is further limited to a valinyl ester prodrug of the 2'-branched nucleoside.

The relevance of Carroll *et al.* is set forth above. The Carroll patent does not disclose amino acid ester prodrug.

Sinko *et al.* disclose valacyclovir (VACV), the L-valyl ester of the acyclic nucleoside analog of deoxyguanosine. Sinko *et al.* further disclose that the mean absolute oral bioavailability of VACV is three to five times that of acyclovir in humans. See page 209, right column, 2nd ¶.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method taught by the Carroll patent so as to replace the 3'-OH group of 2'-branched nucleoside with a valine ester group to make a valinyl

ester prodrug as taught by Sinko *et al.* The skilled artisan would have been motivated to do so to enhance the oral bioavailability of the nucleoside drug. There would have been a reasonable expectation of success, given the success of improving the intestinal uptake of nucleoside analog acyclovir, as taught by Sinko *et al.* Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Correspondence

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey, Ph.D. whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9:30 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Jeffrey Parkin, Ph.D.
Primary Examiner
27 July 2007

Louise Humphrey, Ph.D.
Assistant Examiner